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L3	neural adj tube adj defect or ntd or down$ near3 syndrome or cardiovascular adj (disease or disorder)	15606	L3
L2	(methionine near3 synthase near3 reductase or mtrr)	50	L2
L1	(methionine near3 synthase near3 reductase or mtrr) near8 (mutation or polymorphism)	4	L1

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Search Results - Record(s) 1 through 9 of 9 returned.

1. 20030198985 . 24 Feb 03. 23 Oct 03. Assay for nitrous oxide neurologic syndrome. Hogan, Kirk J., et al. 435/6; C12Q001/68.

2. 20030198970 . 29 Jul 02. 23 Oct 03. Genostics. Roberts, Gareth Wyn. 435/6; 536/24.3 C12Q001/68 C07H021/04.

3. 20030082676 . 10 Aug 99. 01 May 03. HUMAN METHIONINE SYNTHASE REDUCTASE: CLONING, AND METHODS FOR EVALUATING RISK OF NEURAL TUBE DEFECTS, CARDIOVASCULAR DISEASE, AND CANCER. GRAVEL, ROY A., et al. 435/69.1; 435/191 435/320.1 435/325 435/6 536/23.2 C12Q001/68 C07H021/04 C12N009/06 C12P021/02 C12N005/06.

4. 6566065 . 12 Jun 00; 20 May 03. Method of diagnosing schizophrenia by detecting a mutation in the (MTHFR) gene. Rozen; Rima. 435/6; 435/91.2 536/23.7 536/24.31. C12Q001/68 C12P019/34 C07H021/02 C07H021/04.

5. 6528259 . 13 Sep 00; 04 Mar 03. Methods for detecting human methylenetetrahydrofolate reductase allelic variants. Rozen; Rima, et al. 435/6; 435/23 435/91.2 514/1 514/2 536/23.5. C12Q001/68 C12P019/34 C07H021/04 A61K031/00.

6. 6376210 . 06 Jul 99; 23 Apr 02. Methods and compositions for assaying analytes. Yuan; Chong-Sheng. 435/18; 435/195 435/23 435/252.3 435/320.1 435/455. C12Q001/34 C12N009/14 C12N001/20 C12N015/00 C07H021/04.

7. 6218120 . 01 Mar 99; 17 Apr 01. Methods for detecting human methylene tetrahydrofolate reductase allelic variants. Rozen; Rima, et al. 435/6; 435/91.2 536/23.2 536/23.5 536/24.31 536/24.33. C12Q001/68 C12P019/34 C07H021/04.

8. 6210950 . 25 May 99; 03 Apr 01. Methods for diagnosing, preventing, and treating developmental disorders due to a combination of genetic and environmental factors. Johnson; William G., et al. 435/252.3; 435/183 435/320.1 536/23.1 536/24.31 536/24.33. C07H021/04 C07H021/02 C12N001/20 C12N015/00 C12N009/00.

9. 5668173 . 23 Feb 96; 16 Sep 97. Method of increasing the conversion of homocysteine to methionine and uses thereof. Garrow; Timothy A.. 514/557;. A61K031/19.

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Terms	Documents
l4 and l5	9

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(FILE 'HOME' ENTERED AT 19:09:52 ON 13 NOV 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 19:10:12 ON 13 NOV 2003

L1 230 S (METHIONINE(3A)SYNTHASE(3A)REDUCTASE OR MTRR)(8A)(MUTATION OR
L2 183541 S NEURAL(W)TUBE(W)DEFECT OR NTD OR DOWN?(3A)SYNDROME OR CARDIOV
L3 84 S L1 AND L2
L4 2018643 S 66 OR 22 OR 110 OR 1675 OR 1726 OR 535 OR 575 OR 576
L5 23 S L3 AND L4
L6 10 DUP REM L5 (13 DUPLICATES REMOVED)

=> d au ti so ab 1-10 l6

L6 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
IN Gravel, Roy A.; Rozen, Rima; LeClerc, Daniel; Wilson, Aaron; Rosenblatt, David
TI Cloning, **mutations** and sequence of human **methionine synthase reductase** and applications to evaluating risk of **neural tube defects**, **cardiovascular disease**, and cancer
SO U.S. Pat. Appl. Publ., 26 pp., Cont.-in-part of U. S. Ser. 232,028, abandoned.
CODEN: USXXCO
AB The invention features a novel cDNA encoding human methionine synthase reductase. The invention also features a method for detecting an increased likelihood of hyperhomocysteinemia and, in turn, an increased or decreased likelihood of **neural tube defects**, **cardiovascular disease**, or cancer. The invention also features therapeutic methods for treating and/or reducing the risk of **cardiovascular disease**, cancer, or **neural tube defects**. Also provided are the sequences of the human methionine synthase reductase gene and protein and compds. and kits for performing the methods of the invention. The cDNA for human methionine synthase reductase was cloned and sequenced. Northern blots indicated that the methionine synthase reductase gene was expressed to some degree in all tissues but is particularly abundant in skeletal muscle. In addn. to a 3.6 kb band, a 3.1 kb and a faint 6 kb band were detected in brain mRNA. The methionine synthase reductase gene was mapped to human chromosome 5p15.2-p15.3. Two deletion mutations were found in cblE patients: one resulted in deletion of Ile-**576**, the other resulted in a frameshift and premature truncation. Two polymorphisms were also detected: a G/A polymorphism at nucleotide **66** resulting in either Ile or Met at position **22** and a second G/A polymorphism at nucleotide **110** resulting in Tyr or Cys at position 37. Correlation of **methionine synthase reductase** gene **mutations** and risk for **neural tube d fects**, cancer, and **cardiovascular disease** was examd. The present invention claimed a no. of sequences, but the sequence listing was not made available on publication of the patent application.

L6 ANSWER 2 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AU Kluijtmans, Leo A. J.; Young, Ian S.; Boreham, Colin A.; Murray, Liam; McMaster, Dorothy; McNulty, Helene; Strain, J. J.; McPartlin, Joseph; Scott, John M.; Whitehead, Alexander S. [Reprint Author]
TI Genetic and nutritional factors contributing to hyperhomocysteinemia in young adults.
SO Blood, (April 1, 2003) Vol. 101, No. 7, pp. 2483-2488. print.
CODEN: BLOOAW. ISSN: 0006-4971.
AB A modestly elevated total plasma homocysteine concentration (tHcy) is generally accepted as an independent and graded risk factor for various

pathologies, including vascular diseases, **neural tube defects**, Alzheimer disease, and pregnancy complications. We analyzed 5 common functional polymorphisms in enzymes involved in homocysteine metabolism (ie, methylenetetrahydrofolate reductase (MTHFR) 677C>T and 1298A>C, methionine synthase (MTR) 2756A>G, cystathionine beta-synthase (CBS) 844ins68, and methionine synthase reductase (MTRR) 66A>G) in 452 young adults, and quantified their independent and interactive effects on tHcy concentrations. Serum folate, red cell folate, vitamin B12, and tHcy concentrations were significantly influenced by MTHFR 677C>T genotypes. A particularly strong interaction was observed between the MTHFR 677TT genotype and serum folate, which led to a high tHcy phenotype that was more pronounced in males. The genetic contribution to the variance in tHcy was estimated to be approximately 9%, compared with approximately 35% that could be attributed to low folate and vitamin B12. Our study indicates that dietary factors are centrally important in the control of tHcy levels in young adults with additional, but somewhat weaker, genetic effects. These data underscore the potential benefits that may be gained by improving the dietary status of young adults, and provide support for the implementation of folate/B-vitamin food fortification programs.

L6 ANSWER 3 OF 10 MEDLINE on STN DUPLICATE 1

AU Bosco Paolo; Gueant-Rodriguez Rosa-Maria; Anello Guido; Barone Concetta; Namour Fares; Caraci Filippo; Romano Antonino; Romano Corrado; Gueant Jean-Louis

TI Methionine synthase (MTR) 2756 (A --> G) **polymorphism**, double heterozygosity methionine **synthase** 2756 AG/**methionine synthase reductase** (MTRR) **66** AG, and elevated homocysteinemia are three risk factors for having a child with **Down syndrome**.

SO AMERICAN JOURNAL OF MEDICAL GENETICS, (2003 Sep 1) 121A (3) 219-24. Journal code: 7708900. ISSN: 0148-7299.

AB Contradictory findings have been recently published on the evaluation of genetic **polymorphisms** of methylenetetrahydrofolate reductase (MTHFR 677 C-->T) and **methionine synthase reductase** (MTRR **66** A-->G) as risk factors for having a child with **Down syndrome** (DS); however, the influence of polymorphisms of methionine synthase (MTR 2756 A-->G) and of MTHFR 1298 A-->C has never been evaluated. In this study, the risk of being a DS case or having a DS child (case mother) was studied by multiple logistic regression analysis of the independent and combined genotypes and of plasma homocysteine, folates, and vitamin B12 in 92 DS cases and 140 control subjects as well as in 63 case mothers and 72 age-matched control mothers from Sicily. (The MTHFR 677 T allele frequency was not different in DS cases and case mothers, compared to the respective control groups). After adjustment for age, total homocysteine (t-Hcys) and MTR 2756 AG/GG genotype were significant risk factors for having a DS child, with odds ratio (OR) of 6.7 (95% CI: 1.4-32.0, P = 0.016) and of 3.5 (95% CI: 1.2-10.9, P = 0.028), respectively. By comparison, MTR 2756 AG/GG genotype increased significantly the risk of being a DS case, with an OR of 3.8 (95% CI: 1.4-10.5, P = 0.009). The double heterozygosity MTR 2756 AG/MTRR **66** AG was the single combined genotype that was a significant risk factor for having a DS child, with an OR estimated at 5.0 (95% CI: 1.1-24.1), after adjustment for t-Hcys. In conclusion, our results provide evidences that homocysteine and MTR genetic polymorphism are two potent risk factors for mothers to have a DS child in Sicily.
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L6 ANSWER 4 OF 10 MEDLINE on STN DUPLICATE 2

AU Gueant-Rodriguez R M; Rendeli C; Namour B; Venuti L; Romano A; Anello G; Bosco P; Debard R; Gerard P; Viola M; Salvaggio E; Gueant J L

TI Transcobalamin and **methionine synthase reductas** mutated **polymorphisms** aggravate the risk of **neural tube d fects** in humans.

SO NEUROSCIENCE LETTERS, (2003 Jul 3) 344 (3) 189-92.
Journal code: 7600130. ISSN: 0304-3940.

AB The pathogenic mechanism of **neural tube defects** may involve genetic polymorphisms and nutritional factors related to homocysteine metabolism. We evaluated the association of polymorphisms of three genes affecting vitamin B12-dependent remethylation of homocysteine, transcobalamin (TC), methionine synthase (MTR) and MTR reductase (MTRR), combined or not with methylenetetrahydrofolate reductase (MTHFR), with the risk of having **neural tube defect** in 40 children with spina bifida and 58 matched controls from South Italy. MTR 2756 AG/GG, TC 777 CG/GG /MTHFR 677 CC and MTRR **66** GG /MTHFR 677 CC genotypes increased the risk with odds ratios of 2.6 (P=0.046), 2.4 (P=0.028) and 4.5 (P=0.023), respectively. In contrast, MTHFR 677 TT was protective (odds ratio=0.11, P=0.009). In conclusion, genetic determinants affecting the cellular availability or MTRR-dependent reduction of B12 may increase the risk of spina bifida.

L6 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 3

AU Gaughan D J; Kluijtmans L A; Barbaux S; McMaster D; Young I S; Yarnell J W; Evans A; Whitehead A S

TI The **methionine synthase reductase** (**MTRR**) A66G **polymorphism** is a novel genetic determinant of plasma homocysteine concentrations.

SO ATHEROSCLEROSIS, (2001 Aug) 157 (2) 451-6.
Journal code: 0242543. ISSN: 0021-9150.

AB Epidemiological evidence has revealed that an elevated plasma homocysteine level (hyperhomocysteinemia) confers an increased risk of **cardiovascular disease** and **neural tube defects**. Hyperhomocysteinemia is caused by both nutritional (e.g. folate, vitamins B(6) and B(12)) and genetic factors, including functional polymorphisms of key enzymes involved in homocysteine metabolism. One such enzyme, methionine synthase reductase (MTRR), maintains adequate levels of methylcob(III)alamin, the activated cofactor for methionine synthase, which catalyzes the remethylation of homocysteine to methionine. A common **MTRR polymorphism**, i.e. a **66** A-->G substitution specifying an isoleucine to methionine substitution (I22M), was recently identified. To assess the influence of this polymorphism on total plasma homocysteine (tHcy), we undertook a genotype/phenotype analysis in a study population of 601 Northern-Irish men, aged 30--49, for which biochemical and genetic data relevant to folate/homocysteine metabolism had already been acquired. The 66AA genotype has a frequency of 29% in this population. We established that there was a significant influence of MTRR genotype on tHcy ranking (P=0.004) and that the 66AA genotype contributes to a moderate increase in tHcy levels across the distribution [OR 1.59 (95% CI: 1.10--2.25) for the 66AA genotype to be in the upper half of the tHcy distribution, P=0.03]. The homocysteine-elevating effect of the 66AA genotype is independent of serum folate, vitamin B(12) and vitamin B(6) levels. Based on published estimates of the enhanced **cardiovascular disease** risk conferred by defined increments of plasma tHcy, we estimate that 66AA homozygotes have, on average, an approximately 4% increase in **cardiovascular disease** risk compared to 66GG homozygotes. This study provides the first evidence that the **MTRR** A66G **polymorphism** significantly influences the circulating tHcy concentration.

L6 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 4

AU Hassold T J; Burrage L C; Chan E R; Judis L M; Schwartz S; James S J; Jacobs P A; Thomas N S

TI Maternal folate polymorphisms and the etiology of human nondisjunction.

SO AMERICAN JOURNAL OF HUMAN GENETICS, (2001 Aug) 69 (2) 434-9.
Journal code: 0370475. ISSN: 0002-9297.

AB Attempts to identify genetic contributors to human meiotic nondisjunction have met with little, if any, success. Thus, recent reports linking

Down syndrome to maternal **polymorphisms** at either of two folate metabolism enzymes, methylenetetrahydrofolate **reductase** (MTHFR) and **methionine synthase** reductase (MTRR), have generated considerable interest. In the present report, we asked whether variation at MTHFR (677C-->T) or MTRR (66A-->G) might be associated with human trisomies other than trisomy 21. We analyzed maternal **polymorphisms** at MTHFR and **MTRR** in 93 cases of sex-chromosome trisomy, 44 cases of trisomy 18, and 158 cases of autosomal trisomies 2, 7, 10, 13, 14, 15, 16, 18, or **22**, and compared the distributions of genotypes to those of control populations. We observed a significant increase in the MTHFR polymorphism in mothers of trisomy 18 conceptuses but were unable to identify any other significant associations. Overall, our observations suggest that, at least for the sex chromosomes and for a combined set of autosomal trisomies, polymorphisms in the folate pathway are not a significant contributor to human meiotic nondisjunction.

L6 ANSWER 7 OF 10 MEDLINE on STN

AU Kimura F; Florl A R; Steinhoff C; Golka K; Willers R; Seifert H H; Schulz W A

TI Polymorphic methyl group metabolism genes in patients with transitional cell carcinoma of the urinary bladder.

SO MUTATION RESEARCH, (2001 Jun) 458 (1-2) 49-54.
Journal code: 0400763. ISSN: 0027-5107.

AB Because **polymorphisms** in the methyl group metabolism genes methylene-tetrahydrofolate **reductase** (MTHFR), **methionine synthase** (MS), and cystathione beta-synthetase (CBS) affect plasma homocysteine levels and intracellular concentrations of S-adenosylmethionine (SAM), they modify the susceptibility to **cardiovascular diseases** and cancer. Specifically, genome-wide decreased DNA methylation ('hypomethylation') in human cancers might be a consequence of decreased SAM levels. Because hypomethylation is particularly prevalent in transitional cell carcinoma of the urinary bladder (TCC), the genotype distributions for the two each most prevalent MTHFR, MS, and CBS alleles were compared between 165 TCC patients and 150 population controls. The distributions of the MTHFR 677A/V and the MS 919G/D alleles were not significantly different between cancer patients and controls, even after stratification according to age, gender, tumor stage or grade. The CBS 844INS68 allele was slightly less frequent in TCC patients than in controls (q=0.07 versus 0.10), but was rarer among males in both groups. Among the TCC patients, this gender difference was highly significant (Mantel-Haenszel and chi(2)-test P=0.007). No significant difference between TCC patients and controls was found for any combined genotype. Likewise, the extent of DNA hypomethylation determined in 62 carcinoma specimens was not related to the respective genotypes. Thus, on their own, the MTHFR, MS and CBS genotypes do not appear to act upon susceptibility to TCC or influence the extent of DNA hypomethylation in this cancer.

L6 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN

IN Gravel, Roy A.; Rozen, Rima; Leclerc, Daniel; Wilson, Aaron; Rosenblatt, David

TI Human methionine synthase reductase and cDNA and methods for evaluating risk of **neural tube defects**, **cardiovascular disease**, cancer, and **Down**'s **syndrome**

SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2

AB The invention features a novel cDNA encoding methionine synthase reductase. The invention also features a method for detecting an increased likelihood of hyperhomocysteinemia and, in turn, an increased or decreased likelihood of **neural tube defects**, **cardiovascular disease**, **Down**'s **Syndrome** or cancer. The invention also features therapeutic

methods for treating and/or reducing the risk of **cardiovascular disease**, **Down**'s **Syndrome**, cancer, or **neural tube defects**. Also provided are the sequences of the human methionine synthase reductase gene and protein and compds. and kits for performing the methods of the invention. Thus, the cDNA for human methionine synthase reductase was cloned and sequenced. Northern blots indicated that the methionine synthase reductase gene was expressed to some degree in all tissues but is particularly abundant in skeletal muscle. In addn. to a 3.6 kb band, a 3.1 kb and a faint 6 kb band were detected in brain mRNA. The methionine synthase reductase gene was mapped to human chromosome 5p15.2-p15.3. Two deletion mutations were found in cblE patients: one resulted in deletion of Ile-**576**, the other resulted in a frameshift and premature truncation. Two polymorphisms were also detected: a G/A polymorphism at nucleotide **66** resulting in either Ile or Met at position **22** and a second G/A polymorphism at nucleotide **110** resulting in Tyr or Cys at position 37. Correlation of **methionine synthase reductase** gene **mutations** and risk for **neural tube defects**, **Down**'s **syndrome**, and premature coronary artery disease was examd.

L6 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AU Banerjee, Ruma
TI Molecular biology of methionine synthase: Interrelationships with homocysteine and vascular disease
SO Developments in Cardiovascular Medicine (2000), 230, 291-311
CODEN: DCMEDM; ISSN: 0166-9842
AB A review, with **66** refs. Methionine synthase is one of two key enzymes that manages cellular homocysteine and is found in most mammalian tissues. It catalyzes the B12-dependent transmethylation of homocysteine using methyltetrahydrofolate as a Me group donor. The cDNA encoding human methionine synthase has been cloned recently and its sequence has been detd. Catastrophic mutations in methionine synthase are found in the cblG class of patients, and are correlated with severe hyperhomocysteinemia with attendant **cardiovascular diseases**. However, polymorphisms have yet to be found that are correlated with the moderate hyperhomocysteinemia. A mouse knock out of the methionine synthase gene confers an embryonic lethal phenotype, indicating that it is an essential gene. The activity of methionine synthase is also dependent on redox proteins that reactivate oxidized enzyme. The components of this redox pathway have been described recently to be a cytochrome P450-like methionine synthase reductase and sol. cytochrome b5. **Mutations** in **methionine synthase reductase** have been identified in the cblE class of patients and are correlated with severe hyperhomocysteinemia.

L6 ANSWER 10 OF 10 MEDLINE on STN DUPLICATE 5
AU Rozen R
TI Genetic modulation of homocysteinemia.
SO SEMINARS IN THROMBOSIS AND HEMOSTASIS, (2000) 26 (3) 255-61. Ref: 57
Journal code: 0431155. ISSN: 0094-6176.
AB With the identification of hyperhomocysteinemia as a risk factor for **cardiovascular disease**, an understanding of the genetic determinants of plasma homocysteine is important for prevention and treatment. It has been known for some time that homocystinuria, a rare inborn error of metabolism, can be due to genetic mutations that severely disrupt homocysteine metabolism. A more recent development is the finding that milder, but more common, genetic mutations in the same enzymes might also contribute to an elevation in plasma homocysteine. The best example of this concept is a missense mutation (alanine to valine) at base pair (bp) 677 of methylenetetrahydrofolate reductase (MTHFR), the enzyme that provides the folate derivative for conversion of homocysteine to methionine. This mutation results in mild hyperhomocysteinemia, primarily when folate levels are low, providing a rationale (folate supplementation)

for overcoming the genetic deficiency. Additional genetic variants in MTHFR and in other enzymes of homocysteine metabolism are being identified as the cDNAs/genes become isolated. These variants include a glutamate to alanine mutation (bp 1298) in MTHFR, an aspartate to glycine mutation (bp 2756) in methionine synthase, and an isoleucine to methionine **mutation** (bp **66**) in **methionine synthase reductase**. These variants have been identified relatively recently; therefore additional investigations are required to determine their clinical significance with respect to mild hyperhomocysteinemia and vascular disease.

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L6 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:493687 CAPLUS
DN 133:115929
TI Human methionine synthase reductase and cDNA and methods for evaluating risk of **neural tube defects**, **cardiovascular disease**, cancer, and **Down**'s **syndrome**
IN Gravel, Roy A.; Rozen, Rima; Leclerc, Daniel; Wilson, Aaron; Rosenblatt, David
PA McGill University, Can.
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000042196	A2	20000720	WO 2000-IB209	20000114
	WO 2000042196	A3	20010125		
	W: CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 2003082676	A1	20030501	US 1999-371347	19990810
	CA 2360555	AA	20000720	CA 2000-2360555	20000114
PRAI	US 1999-232028	A	19990115		
	US 1999-371347	A	19990810		
	US 1998-71622P	P	19980116		
	WO 2000-IB209	W	20000114		

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